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10/522,037	04/18/2005	Renaud Nalin	BKR.137T	6742

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EXAMINER	
LIU, SUE XU	

ART UNIT	PAPER NUMBER
1639	

NOTIFICATION DATE	DELIVERY MODE
01/25/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slspatents.com

Office Action Summary	Application No.	Applicant(s)	
	10/522,037	NALIN ET AL.	
	Examiner	Art Unit	
	SUE LIU	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-66* is/are rejected.

7)☒ Claim(s) *66* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/28/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/6/09 has been entered.

Claim Status

2. Claims 1-47 have been cancelled.

Claims 50-66 have been added.

Claims 48-66 are currently pending.

Claims 48-66 are being examined in this application.

Election/Restrictions

3. Applicant's election with traverse of Group I in the reply filed on 4/16/07 is as previously acknowledged.

4. The newly added claims 50-66 are grouped with the previously elected Group I invention.

Priority

5. This application is filed under 35 U.S.C 371 of PCT/EP03/07765 (filed on 07/17/2003), and claims foreign priority to EP 022918718 (7/17/2002).

Information Disclosure Statement

6. The IDS filed on 7/28/09 has been considered. See the attached PTO 1449 forms.

Claim Objection(s) / Rejection(s) Withdrawn

7. All previous claim Objection(s) / Rejection(s) as set forth in the previous Office action (mailed 4/30/08) that are not repeated and/or maintained in the instant Office action are withdrawn.

New Claim Objection(s) / Rejection(s)

Claim Objections

8. Claim 66 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 66 is not further limiting claim 48 because claim 66 recites the same limitation as claim 48.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 53 and 66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 53 recites "the origin of transfer is functional in E. coli host cells", which is unclear and indefinite. The instant claim 48 (from which claim 53 depends) recites the host cells is "a microorganism or host cell other than E. coli" and the "origin of transfer" is used for insertion into the "host cell" other than E. coli. That is the said recitation in claim 53 conflicts with the limitations in claim 48. Thus, the instant claim 53 is indefinite.

Claim 66 recites "said environmental DNA fragments are cloned in E. coli", which seems to recite that the DNA fragment is cloned in E. coli host cells. The instant claim 48 (from which claim 66 depends), however, recites the host cells cannot be E. coli cells. The instant claim 48 only recites the DNA fragments are inserted into E. coli vectors (not E. coli cells). Thus, the recitation of claim 66 is confusion and renders the claim indefinite.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rondon and Others

12. Claims 48-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Rondon** et al (Applied and Environmental Microbiology. Vol. 66(6): 2541-2547; 06/2000; cited in IDS), in view of **Hoang** et al. (Plasmid. Vol.43: 59-72; 2000), **Chain** et al (Journal of Bacteriology. Vol.182: 5486-5494; 10/2000), **Groth** et al (PNAS. Vol.97: 5995-6100; 2000), **Berg** et al (PNAS. Vol.79: 2632-2635; 1982), and if necessary in view of **Devine** et al (US 5,728,551; 3/17/1998) and **Martinez** et al. (PGPUB 20030143745; 7/31/03; earlier priority 11/15/2001).

The instant claims recite "A method for the identification or cloning of polynucleotides… comprising (i) cloning environmental DNA fragments into *E. coli* cloning vectors… (ii) identifying or selecting cloning vectors in said library… (iii) inserting a target polynucleotide construct… (iv) transferring said modified cloning vectors… into… recipient host cell… (v) identifying or cloning the DNA fragments… wherein said environmental DNA fragments are cloned in E. coli an said selected recipient host cell is a microorganism or host cell other than *E. coli*."

Rondon et al, throughout the publication, teach molecular cloning of DNA isolated from microbial samples using various cloning vectors (Abstract).

For **claim 48** *"(i) cloning environmental DNA fragments into E. coli cloning vectors…"* The reference teaches construction BAC (bacterial artificial chromosome) libraries made with DNA isolated directly from soil (e.g. p.2541, right col., para 2; p.2542, left col., para 1-2), which read on step (i).

"(ii) identifying or selecting cloning vectors in said library..." The reference also teaches screening and analyzing the clones from the generated libraries (e.g. pp.2542-2543; especially bridging para) and selection of a certain constructs such as the constructs that contain various genes (including cellulose, chitinase, keratinase, etc.) (e.g. p.2543), as well as "selecting" DNA with certain size from the generated libraries (e.g. p.2542, left col., para 3), which read on the "selecting step" (step (ii)).

"(iii) inserting a target polynucleotide construct..." The reference also teaches restriction digestion of the selected vectors, and then subsequent ligation and transformation of the selected DNA (e.g. p.2542, cols, 1-2), which reads on the "transferring" and "cloning" steps.

"(iv) transferring said modified cloning vectors... into... recipient host cell...": The reference also teaches restriction digestion of the selected vectors, and then subsequent ligation and transformation of the selected DNA (e.g. p.2542, cols, 1-2), which reads on the "transferring" and "cloning" steps. The reference also teaches "integrating" the DNA of interest into a DNA molecule comprised by the host cells.. The reference teaches mutating BAC (i.e. chromosome) of host cells (e.g. p.2541, last para; p.2542, right col., para 5; pp.2452+) as described in a related publication, Rondon et al (PNAS. Vol.96: 6451-6455; 1999), which the "integration" (or transposon mutagensis) procedure of Rondon (2000) is the carried out the same as the one in Rondon (1999). The Rondon (1999) publication teaches transforming BAC containing host cells (i.e. "chromosome" containing host cells) with plasmids (or DNA vectors) for transposon mutations (e.g. pp.6452-6453 of Rondon (1999)). Thus, by using the transposon mutagensis procedure, one of the host cell "chromosome" (i.e. the transformed BAC) is integrated with "the polynucleotide" from the inserted cloning vector.

"(v) identifying or cloning the DNA fragments…": The reference also teaches sequencing the cloning vector as well analyze the encoded proteins (e.g. p.2542), which read on the last step.

For **claim 49**: The reference teaches constructing DNA fragment libraries using BAC vectors (bacterial artificial chromosome) (e.g. p.2541, right col., para 2; p.2542, left col., para 1-2).

For **claims 50** and **51**: The reference teaches construction BAC (bacterial artificial chromosome) libraries made with DNA isolated directly from soil (e.g. p.2541, right col., para 2; p.2542, left col., para 1-2).

For **claim 56**: The reference also inherently teaches the cloning vectors to have at least a promoter region as recited in claim 56, because the cloned DNA fragments are successfully expressed (e.g. pp.2542-2543) indicating a promoter region for transcriptional gene expression activation.

For **claim 60**: The reference teaches screening the bacterial DNA using various molecular techniques (e.g. pp.2542+).

For **claim 62**: The reference teaches identifying nucleic acid sequences and/or activities of the isolated DNA (e.g. pp.2542+).

For **claims 63** and **64**: The reference teaches various insertion DNA fragment sizes including 27 kb (p.2542, last para), 50 kb, 76 kb, etc. (e.g. p.2543). It would also have been prima facie obvious to generate DNA fragments with sizes ranging from 40 to 80 kb in length, because the Rondon reference teaches it is predictable to substitute DNA fragments with one size for others as it depends on routine experimental design.

Rondon et al do not explicitly teach the "a target polynucleotide construct" comprising origin of transfer" and an "integrase functional" as recited step (ii) of **clm 48** and integration into a genome of the host cells as recited in **clms 48**, **52**, **65** and **66**. The reference also does not explicitly teaches the target polynucleotide construct comprises the "origin of transfer functional" as recited in **clms 53** and **54**, as well as the inherent function of conjugative transfer as recited in **clm 61**. The abbreviation, RP4 recited in **clm 54** is construed as referring to the bacterial plasmid RP4. The reference also does not explicitly teach the specific integrase recited in **clm 55**. The reference also does not explicitly teach the target polynucleotide construct is contained in a "transposable nucleic acids" as well as using "transposase" for cloning vector modification as recited in **clms 57-59**. The reference also does not explicitly teach the host cell has a "genomic distinct from E. coli" as recited in **clm 48**.

However, **Hoang** et al., throughout the publication, teach methods of using vectors containing OriT and integrase to integrate desired DNA into genome of host cells (e.g. Abstract). The reference teaches using plasmids having OriT and an integrase encoding gene (e.g. Figure 1), which construct reads on the target polynucleotide construct of **clm 48**. The reference also teaches transferring desired DNA from *E. coli* to *Pseudomonas aeruginosa* (e.g. Abstract; p.62, left col. last para), which reads on the transfer as recited in **clm 48**. The reference also teaches integrating the DNA into the genome of *P. aeruginosa* (e.g. p.63, right col.), which reads on the genomic integration as well as the host cells of **clms 48** and **66**. The reference also teaches the integration is site specific (e.g. Abstract; title) as recited in **clm 52**. The reference also teaches OriT (e.g. p.63, left col.), which reads on the product by process limitation of **clm 54** as well as the inherent function of **clm 53**. The reference teaches using phage integrase (CTX). The

reference also inherently teaches "conjugative transfer" recited in **clm 61**, because "conjugative transfer" is an inherent property or a "natural DNA transfer mechanism" of constructs comprising "origin of transfer" (such as oriT from RP4) as evidenced by the instant specification (instant spec. p.14, lines 25+). The reference also teaches the integration is a stable integration (e.g. p.69, last para), which reads on the limitation of **clm 65**. The reference also teaches the advantages of using such a DNA transfer/integration system (especially into other host cells than E. coli) such that an efficient and stable system can be used to study genes with unknown functions (e.g. p.59 ; p.69).

Chain et al, throughout the publication, teach inserting oriT from RK2 (equivalent to RP4) into cloning vectors for site specific recombination of fragments of bacteria genomic DNA isolated from environment (such as soil) (e.g. Abstract; p.5484, Figures 1-2), which read on the origin of transfer (RP4) as recited in **clms 53** and **54**. The reference also inherently teaches "conjugative transfer" recited in **clm 61**, because "conjugative transfer" is an inherent property or a "natural DNA transfer mechanism" of constructs comprising "origin of transfer" (such as oriT from RP4) as evidenced by the instant specification (instant spec. p.14, lines 25+). In addition, the Chain reference also teaches the inherent property of conjugative transfer of the oriT element (Chain, p.5486, right col., para 2; p.5491, right col., para 1). The Chain reference also teaches the oriT is inserted in a position that is "distinct" from other inserted DNA fragments (e.g. Figure 1), which reads on the "distinct" insertion as recited in **clm 48**.

Groth et al, throughout the publication, teach inserting using phage C31 integrase to carry out recombination between DNA or interest and bacterial chromosome or human DNA (e.g. Abstract; pp.5995-5996), which reads on the phage C31 integrase of **clm 55**. The reference

also teaches using human cells as host cells (e.g. Abstract), which reads on the host cells of **clms 48**. The reference also teaches the advantages of using host cells such as human cells (that is distinct from the E. coli cells) so that a broad range of genetic engineering applications can be carried out (e.g. Abstract).

Berg et al, throughout the publication, teach inserting using transposon elements for modifying DNA constructs (Abstract). The reference teaches the transposon DNA comprising inverted repeats, and marker gene such as Kan resistance gene (e.g. Figures 1-2). The reference also teaches using transposase for the DNA recombination process (e.g. p.2632, para 1; pp.2633-2634, bridging para). The reference also teaches inverse transposition where the Kan resistance gene is replaced by other drug resistance genes (e.g. Figure 2), which read on the reagents and/or method steps of replacing the first marker gene with the second marker gene as recited in **clms 57-59**. The reference also teaches the advantages of using transposons such as their ability to recombine DNA without needing extensive DNA homology (e.g. p.2632, para 1).

Devine et al, throughout the patent, teach using transposons (with transposase) to facilitate DNA recombinant events (Abstract). The reference also teaches the advantages of "in vitro" transposon reactions such as high efficiency and versatility of the method (e.g. col. 5, lines 45+).

In addition, **Martinez** et al., throughout the publication, teach using various cloning and/or integrating vectors to insert DNA fragments of interests into the genome of host cells other than E. coli such as Streptomyces (e.g. Abstract). The reference specifically teaches using vectors containing a cassette comprising OriT (from RP4) and phage C31 integrase (e.g. [0123]).

The reference also teaches the need and advantages of generating vectors to integrate DNA of interests into host cells such as Strep. (e.g. [0002]+).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to insert "oriT" derived from RP4 or other plasmid into cloning vectors through the "natural DNA transfer mechanism" as well as inserting an integrase coding gene (such as phage C31 integrase) for the purpose of integrating the desired DNA into the host cell genome. It would also have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to use transposon with transposase for desired DNA recombination such as insertion, deletion or mutation of DNA constructs in an in vitro or in vivo process.

A person of ordinary skill in the art would have been motivated at the time of the invention to insert a cassette having OriT (or other origin or transfer) and a gene encoding for an integrase to a vector (having DNA of interest) and using the vector to integrate the DNA of interest into the genome of the desired host cells (through conjugative transfer), because Hoang et al teach the need to generate such a vector (having both OriT and integrase gene) so that stable and efficient DNA integration into host cells (other than E. coli) can be achieved (especially useful for studying DNA with unknown function) as discussed supra. If necessary, Martinez et al, also teach the need to make and use such a vector so the host cell range for studying DNA of interest can be easily done. Thus, it would have been obvious to one of ordinary skill in the art to apply the standard technique of inserting a cassette containing DNA integration elements including OriT and genes encoding for integrase elements as taught by Hoang and others, to

improve the DNA transfer vector system for the predicable result of enabling standard DNA cloning and integration into the desired host cells.

A person of ordinary skill in the art would have been motivated at the time of the invention to insert oriT (or the origin of transfer) from RP4 plasmid in cloning or expression vectors, because utilization of these oriT DNA fragments offers the advantages of specific site direct insertion of large fragments from bacteria genome to host E. coli genome as taught by Chain et al (e.g. Abstract). It would have been obvious to one of ordinary skill in the art to apply the standard technique of addition of an origin of transfer in cloning vectors such as taught by Chain et al, to improve the vector system for the predicable result of enabling standard DNA cloning and recombination.

A person of ordinary skill in the art would have been motivated at the time of the invention to include nucleic acids encoding for the phage C31 integrase in the cloning or expression vector for the purpose of integrating the desired DNA, because utilization of integrase offers the advantages of "precise unidirectional integration" with high efficiency as taught by Groth et al (e.g. Abstract). It would have been obvious to one of ordinary skill in the art to apply the standard technique of addition of an integrase encoding gene in cloning vectors such as taught by Groth et al, to improve the vector system for the predicable result of enabling standard DNA cloning and recombination especially for integration into the cellular chromosome.

A person of ordinary skill in the art would have been motivated at the time of the invention to use transposons with transposase for either in vivo or in vitro recombining DNA to generate desired DNA constructs, because utilization of transposons/transposase especially in an in vitro process offers the advantages of DNA recombination without requiring DNA homology

as taught by Berg et al, and high efficiency in an in vitro process as taught by Devine et al discussed above. It would have been obvious to one of ordinary skill in the art to apply the standard technique of addition of using transposons with transposases for recombining DNA such as taught by Berg and Devine, to improve the in vitro DNA recombining process for the predicable result of enabling standard DNA cloning and recombination.

A person of ordinary skill in the art would have been motivated at the time of the invention to use cells that are distinct from E. coli as host cells, because Groth et al. teach the advantages of using other host cells (such as human cells) so that a broad range of genetic applications can be carried out. In addition, because the cited references (such as Haldimann and Groth) teach methods of cloning using integrase function in various cells, it would have been obvious to one skilled in the art to substitute one host cell for the other to achieve the predictable result of cloning DNA of interest using known and routine molecular cloning technologies.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since Rondon et al, Chain et al and Groth et al have demonstrated manipulation of various cloning vectors for insertion of desired DNA fragments such as oriT, phage C31 integrase, nucleic acid fragment of interest, and host cell transformation as well as conjugative transfer are routine and known in the art and have shown to be successfully used for various molecular cloning processes. In addition, Rondon et al, Chain et al, Groth et al, Berg et al and Devine have demonstrated manipulation of various cloning vectors for insertion of desired DNA fragments using various elements such as transposons are routine and known in the art and have shown to be successfully used for various molecular cloning processes.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUE LIU whose telephone number is (571)272-5539. The examiner can normally be reached on 9am-4pmpm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SUE LIU/
Primary Examiner, Art Unit 1639
1/5/2010